Clinical Profile and Comparison of Causality Assessment Tools in Cutaneous Adverse Drug Reactions

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Abstract

Background: Cutaneous adverse drug reactions (CADRs) are probably the most frequent of all manifestations of drug sensitivity. As a considerable number of new drugs are periodically introduced into the market, the incidence of CADR is likely to increase. The pattern of CADR and the causative drugs is likely to change accordingly. There is no uniformly accepted and reliable method of objectively assessing the causal link between drug and adverse reaction. **Aim:** To study the clinical patterns and causative drugs and compare causality assessment [World Health Organization (WHO) and Naranjo algorithm] of CADR among patients attending the dermatology department. **Materials and Methods:** This is a cross-sectional hospital-based study in which all patients with suspected CADR attending the dermatology department of a tertiary care center over a 9-month period were evaluated using the causality assessment criteria recommended by the WHO-Uppsala Monitoring Centre (UMC) and Naranjo scale. The severity of the reaction was assessed using Adverse Drug Reaction Severity Assessment Scale (modified Hartwig and Siegel scale). **Results:** A total of 200 consecutive patients with CADR were evaluated. The causality assessment for a drug as per WHO scale yielded 63 (31.5%) cases as certain, 12 (6%) as probable, and 125 (62.5%) as possible, whereas Naranjo scale showed 26 (13%) cases to be definite, 138 (69%) as probable, and 36 (18%) as possible. There was poor agreement between the two scales. Fixed drug eruption was the most common pattern of CADR (82.41%). The average number of drugs received by patients was 2.09. The most common suspected drug group was antimicrobials (n = 170; 40.5%), followed by nonsteroidal anti-inflammatory drugs (n = 148; 35.3%) and antiretroviral drugs (n = 41; 9.7%). Fixed drug eruption was most commonly caused by paracetamol. Antiepileptics and antimicrobials were the most common suspects among severe cutaneous adverse reactions. **Limitations:** Multiple concomitant drug usage by patients and inability to provoke all patients/measure drug levels in blood resulted in higher number of drugs with causal association as probable/possible. **Conclusion:** WHO-UMC scale was found to be easier to apply and evaluate, with greater practical utility. Poor agreement between the two commonly used scales emphasizes the need for a consistent and uniform causality assessment tool.

Keywords: *Causality assessment, cutaneous adverse drug reactions, oral rechallenge*

Introduction

Adverse reactions to drugs are an inevitable price paid by mankind for the vast benefits of modern medicine. An adverse drug reaction is a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man.[1] Cutaneous adverse drug reactions (CADRs) are probably the most frequent of all manifestations of drug sensitivity comprising 10%–30% of all reported adverse drug reactions.[2] The incidence of CADRs is estimated at 0.16%–3.3% in hospitalized patients, 0.14% in non-hospitalized patients, and 0.25% in the general population.[3] The spectrum of CADRs is very wide and any skin disorder can be imitated, induced, or aggravated by drugs.

Causality assessment is the evaluation of the likelihood that a particular treatment is the cause of an observed adverse event, and establishing a causal association between a drug and a drug reaction is necessary to prevent further recurrences.[4] Numerous methods available for establishing causal association between the drug and adverse event have been broadly classified into clinical judgment or global introspection, algorithms, and probabilistic methods. These include the Swedish method, World Health

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Organization-Uppsala Monitoring Centre (WHO-UMC) scale, Naranjo's algorithm, Kramer algorithm, Jones algorithm, Karch algorithm, Bégaud algorithm, Adverse Drug Reactions Advisory Committee guidelines, Bayesian Adverse Reaction Diagnostic Instrument, and so on.[5] In spite of various methods available, none of the causality assessment tools have been universally accepted as the gold standard. Naranjo's algorithm and WHO-UMC scales are, however, most commonly used.

As a considerable number of new drugs are periodically introduced into the market and being prescribed, the incidence of CADRs is likely to increase. The pattern of cutaneous adverse drug eruptions and the drugs responsible for them is likely to change accordingly. A standardized approach is necessary to establish causality to result in an accurate identification of ADRs in today's era of polypharmacy. Knowledge of drugs that can cause CADRs and a uniform, reproducible causality assessment can help physicians in choosing safer drugs and therefore can be helpful to society at large. Therefore, we conducted this study with the objectives of studying the clinical patterns and causative drugs and comparing the two most commonly used causality assessment methods – Naranjo's algorithm and WHO-UMC scales.

Materials and Methods

This is a cross-sectional hospital-based study wherein all the clinically suspected cases of CADRs attending the dermatology department of a tertiary care center over a 9-month period were evaluated. These included both in-patients and out-patients and those who were referred from other departments. The inclusion criteria were patients of all age groups and both sexes with suspected CADRs and those willing to give written informed consent. Patients with unknown drug details, unclear drug history, reactions to topical application of drugs, and indigenous medications were excluded. Demographic data, illness prompting drug intake, detailed drug history, time sequence of events, symptoms, pattern of rash, history of previous drug reaction, and comorbidities were recorded in a CADR reporting form. As per WHO, a drug reaction is considered serious if that results in death, requires hospitalization or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life-threatening. The CADRs considered under the serious CADR category were Stevens–Johnson syndrome (SJS), SJS/toxic epidermal necrolysis (TEN), TEN, drug hypersensitivity syndrome (DHS), erythroderma, and acute generalized exanthematous pustulosis. Laboratory tests were performed only in serious CADRs. Effect of withdrawal of the suspected drug (dechallenge) was noted in all patients and rechallenge was carried out where feasible. Drug levels could not be measured due to unavailability of the facility.

The patients presenting to our center with cutaneous adverse reactions to drugs were counseled about provocation tests and those who gave consent were taken up for rechallenge. Patients with serious CADRs were excluded and not offered the provocation test. The patients enrolled for rechallenge were told to report after 4 weeks of subsidence of symptoms. This was done to cover five times a period of the elimination half-life. On subsequent visit, the patient was admitted to the dermatology ward for testing under 24 h supervision of a resident doctor. The procedure was started with the least suspected drug moving on to the most suspected drug. Initially, one-fourth of the therapeutic dose of the drug was given followed by half the therapeutic dose and then full therapeutic dose, each at an interval of 24 h. If still there was no reaction, on the fourth day the patient was given 1 day's full therapeutic dosage. The drug was stopped as soon as the first objective symptoms occurred. If still there was no reaction, the drug was considered safe. An interval of 1 day was given before the next drug. If some drugs remained for testing, the patient was readmitted after 1 month and tested for the remaining drugs.

The causality assessment criteria recommended by the WHO-UMC[6] and Naranjo[7] were followed. The agreement between two ADR causality scales was assessed using weighted kappa (*K*) test using SPSS 16 software.

The severity of the reaction was assessed using modified Hartwig and Siegel ADR Severity Assessment Scale.[8] As per the scale, the level of severity of CADRs was classified as levels 1–7. Levels 1 and 2 indicate mild, levels 3, 4a, and b moderate, and levels 5, 6, and 7 severe grade.

Observations

The demographic and clinical profile of the patients with CADRs is given in Table 1 and Figures 1-4 respectively.

A total of 419 drugs were suspected to be responsible for occurrence of CADRs in 200 patients. The average number of drugs consumed by patients was 2.09. The most common groups of suspected drugs responsible for CADRs were antimicrobial drugs (40.5%) followed by nonsteroidal anti-inflammatory drugs (NSAIDs; 35.3%) and antiretroviral drugs (9.7%). Table 2 shows the commonly suspected drugs in various CADRs.

The causality assessment for a drug as per WHO scale yielded 63 (31.5%) cases as certain, 12 (6%) as probable, and 125 (62.5%) as possible, whereas Naranjo scale showed 26 (13%) cases to be definite, 138 (69%) as probable, and 36 (18%) as possible.

Rechallenge was carried out in 32 (16%) patients with nonserious CADRs by oral route. It was positive in 25 (78.12%) and negative in 7 patients. Table 3 shows the results of rechallenge.

Discussion

In this cross-sectional hospital-based study, age group 20–39 years (112; 56%) was the most commonly affected by CADRs as reported by other studies.[9,10] There was a male

Table 1: Demographic profile of patients with cutaneous adverse drug reactions

Demographic characteristics	Distribution of patients
Percentage of CADRs among dermatology patients	0.25% (200 of 78,708 patients)
Sex distribution	Males 112, females 88
Age distribution	4 to 95 years, mean age of 32.81±14.1 years
Most commonly affected age groups	Age group 20-39 years (*n*=112; 56%)
	Age group 40-59 years (*n*=49; 24.5%)
Severity	Nonserious 171 (85.5%), serious 29 (14.5%)
Common CADR patterns	Fixed drug eruption (*n*=82, 41%)
	Urticaria/angioedema (*n*=43, 21.5%)
	Maculopapular rash (*n*=29, 14.5%)
	SJS/TEN spectrum (*n*=14, 7%)
Latency period to drug intake	Less than 24 h (*n*=80, 40%)
	1-3 days (*n*=61, 30.5%)
	>3-7 days (*n*=23, 11.5%)
	>1-3 weeks (*n*=18, 9%)
	>3 weeks (*n*=17, 8.5%)
Past history of drug reaction	81 of 200 (40.5%)
Associated comorbidities	34 (17%), most common - HIV infection (23, 11.5%)
Severity grading as per the modifiedHartwig scale	Mild grade (*n*=12, 6%)
	Moderate grade (*n*=156, 78%)
	Severe grade (*n*=32, 16%)

CADR: Cutaneous adverse drug reaction; SJS: Stevens-Johnson syndrome; TEN: Toxic epidermal necrolysis

Figure 1: Maculopapular rash

Figure 2: Fixed drug eruption

preponderance in our study which has been noted previously by other workers as well.[9-12] However, a few other studies[13-15] have reported females to be affected more commonly.

The majority of serious CADRs developed after more than a week of drug intake. Huang *et al.*[13] also reported longer latency period with severe reactions. DHS (6/6; 100%) and SJS/TEN (9/14; 64.2%) developed after 1–3 weeks or more of drug intake. DHS is known to have a longer latent period and rash appearing >3 weeks after drug intake is one of the diagnostic criteria as per Japanese Research Committee on Severe Cutaneous Adverse Reaction.[16] A relatively lower percentage of history of drug allergy recorded in SCAR could possibly be due to more caution leading to strict avoidance of the suspected/offending drug. Among patients with comorbidities (*n* = 34; 17%), the most common associated entity was HIV positivity (23/34; 67.6%).

Among the various patterns of CADR observed, fixed drug eruption was the most common pattern, followed by

urticaria and maculopapular rash (MPR). This is similar to observations in some other studies.[9,12,17-19] Patel and Marfatia[12] studied 200 patients and reported FDE in majority (61; 30.5%), followed by urticaria (37; 18.5%) and MPR (36; 18%), a finding almost similar to ours. However, a few studies[10,11,14] have reported MPR to be the most common pattern. Hiware *et al.*,[10] in a study on 872 patients over 4 years, observed MPR as the commonest CADR (329; 37.7%), followed by FDE (150; 17.2%) and urticaria (127; 14.5%).

Figure 3: Drug hypersensitivity syndrome

Huang *et al.*[13] reported 109 (14.8%) SCAR out of 734 in-patients. The percentage of SCAR in our study (14.5%; 29/200) is similar to this study. However, Huang *et al.*[13] included only SJS, TEN, and exfoliative dermatitis as SCAR. A lower incidence (6.6%) of SCAR was noted by Sharma *et al.*[9] Hiware *et al.*[10] also noted

Figure 4: Toxic epidermal necrolysis

Table 2: Most commonly suspected drugs in various CADRs

Drugs (% of all drugs suspected)	FDE (*n*=82)	Urticaria and angioedema (*n*=43)	MP rash (*n*=29)	DHS (*n*=6)	AGEP (*n*=5)	Erythroderma (*n*=4)	SJS/TEN spectrum (*n*=14)
Anti-microbial drugs (40.5%)	Ofloxacin	Ofloxacin	Cotrimoxazole		Amoxycillin	Cotrimoxazole	Amoxycillin
	Ornidazole	Ornidazole	Amoxycillin		Cefpodoximee	Azithromycin	Albendazole
	Ciprofloxacin	Amoxycillin	Griseofulvin		Griseofulvin		Azithromycin
NSAIDs (35.3%)	Paracetamol	Paracetamol	Paracetamol		Paracetamol		Diclofenac
	Ibuprofen	Ibuprofen	Diclofenac		Ibuprofen		Paracetamol
	Nimesulide	Diclofenac	Ibuprofen				
Anti-retroviral drugs (9.7%)		Lamivudine	Lamivudine			Zidovudine	
		Efavirenz Tenofovir	Tenofovir			Lamivudine	
			Efavirenz			Nevirapine	
Anti-epileptic drugs (3.3%)			Phenytoin	Carbamazepine		Carbamazepine	Phenytoin
				Phenytoin			Carbamazepine
				Allopurinol			Lamotrigine
Antitubercular drugs (2.1%)					Rifampicin	Isoniazid	
						Rifampicin	
						Ethambutol	
Others (9.1%)	Cetirizine	Omeprazole	Levamisole		Dapsone		Omeprazole
	Levocetirizine	Albendazole					

FDE: Fixed drug eruption; MP rash: Maculopapular rash; DHS: Drug hypersensitivity syndrome; AGEP: Acute generalized exanthematous pustulosis; SJS/TEN: Stevens-Johnson syndrome/toxic epidermal necrolysis; NSAID: Nonsteroidal anti-inflammatory drug

Table 3: Results of rechallenge

CADR pattern (no. of patients)	Drugs confirmed on rechallenge
FDE (*n*=19)	Ciprofloxacin, cetirizine, tinidazole, ornidazole, cotrimoxazole, nimesulide, norfloxacin, ofloxacin, ibuprofen, paracetamol
MPR (*n*=4)	Nevirapine, lamivudine
Urticaria (*n*=2)	Lamivudine, ornidazole

CADR: Cutaneous adverse drug reaction; FDE: Fixed drug eruption; MPR: Maculopapular rash

only 17 (1.95%) out of 872 patients with CADRs as serious, comprising SJS, anaphylaxis with angioedema, and DHS. Choon and Lai[11] reported a very high occurrence of SCAR (144/362; 39.7%) although they included only DRESS and SJS/TEN spectrum. Moderate grade of CADR has been reported to be more common by Shah *et al.*[17] (96.5%; 138/143). In our study too, this grade was found to be more common (78%; 156/200).

Multiple drug usage has become a major problem causing hindrance in ascertaining the culprit drug. Our 74% patients had received multiple drugs simultaneously. Huang *et al.*[13] also found 58.8% CADR due to multiple drugs. The average number of drugs received by our patients was 2.09 with a range of minimum of one drug to a maximum of six drugs. Thakkar *et al.*[20] observed an average of 2.46 drugs per patient.

The most common drug group associated with occurrence of CADR was antimicrobials followed by NSAIDs, an observation similar to many other studies.[10,15,21,22] A number of studies[9,12,14,18] have also reported antimicrobials as the commonest agents. The third most common group implicated was antiretroviral drugs in contrast to steroids reported by Sharma *et al.*[10] and Hiware *et al.*,[11] and antiepileptics reported by Akpinar *et al.*[15] The most common group of antimicrobials found to be associated was flouroquinolones (FQ) as also reported by Thakkar *et al.*,[20] Chopra *et al.*;[14] however, they found beta lactams to be common offenders. FQ have been reported to be a frequent offender in a large number of studies[15,20-24] possibly due to unsupervised over-the-counter (OTC) dispensing of FQ for diarrhea. Among the antimicrobials, the most common offending drug was ofloxacin in contrast to tinidazole reported by Sharma *et al.*[10] and amoxicillin by Akpinar *et al.*[15] Among NSAIDs, paracetamol was the most common drug as also reported by Sharma *et al.*[10] This could be attributed to the fact that paracetamol is commonly included in many anti cold and analgesic preparations, and is widely used/abused as OTC product because it is generally considered safe among other available antipyretics and analgesics. The most common suspected drug was paracetamol (70/419; 16.7%) in consonance with Padmavathi *et al.*[19] but in contrast to cotrimoxazole reported by Hiware *et al.*[11] and allopurinol by Huang *et al*.[13]

Oral provocation or drug rechallenge is the gold standard method to ascertain causality in CADRs. Patients who underwent rechallenge included those with FDE (21/200; 10.5%), MPR (8/200; 4%), and urticaria (3/200; 1.5%). It was positive in 78.1% (25/32) and negative in 21.9% (7/32) patients. Patel and Marfatia[13] carried out rechallenge in 40 cases with 29 (72.5%) cases giving positive results. Kaimal and Madhukara[25] in their study of oral provocation test on patients with CADRs to antiretroviral/antitubercular drugs followed a rechallenge protocol similar to this study. Some of the causes for negative rechallenge could be absence of crucial cofactors during the test procedure (light, comedication, viral infection, physical exercise), desensitization caused during testing, and refractory period after the reaction.

Causality assessment in our study was done using two scales (WHO and Naranjo). The WHO scale yielded 31.5% (63) certain, 6% (12) probable, and 62.5% (125) possible cases. Using the same scale, Shah *et al.*[18] in a study on 143 patients found 2% certain, 23% probable, and 46% possible cases. Thakkar *et al.*[20] found the distributions of "certain," "probable," and "possible" categories as 2.92%, 35.08%, and 38.01%, respectively, in their study. The Naranjo scale showed 13% (26) definite, 69% (138) probable, and 18% (36) possible cases. Chopra *et al.*[14] reported certain association in 1.4%, possible in 34.1%, and probable in 64.5% using the same scale. A higher number of probable cases (77.3%) using the Naranjo scale has also been reported by Sharma *et al.*[10] A higher number of certain/definite causality assignment in our study using both the scales can be attributed to the rechallenge performed as it clarifies a drug's association with the CADR, especially in cases of simultaneous multiple drug consumption.

On comparing the WHO and Naranjo scales, we found that the outcome of causality association in terms of certain/definite and probable did not match with each other (WHO/Naranjo – certain/definite 31.5%/13%, probable 6%/69%). This discordance between the two scales could be accounted for by the differing parameters that are used for assigning a drug reaction into different categories as certain/definite, probable, and possible. In Naranjo scale, for assigning a CADR into definite/probable category, more stringent and objective parameters such as placebo and drug readministration details, toxic drug levels in body, and confirmation by objective evidence need to be fulfilled. On comparing the two scales, we found "poor" agreement between Naranjo and WHO-UMC with Kappa statistic value of 0.174 (*K*-value 0.01–0.20 denotes poor agreement).

Behelkar *et al.*[4] also found "poor" agreement between Naranjo and WHO-UMC scales (Kappa statistic = 0.143) with WHO-UMC scale found to be simpler and less time-consuming. It has been found that the ability of algorithms to establish causality in ADRs is undermined

by confounding variables and no method is universally accepted.[26] In another study, which aimed to compare interrater and multirater agreement for ADR causality assessment using 10 different algorithms, none of the algorithms showed 100% reproducibility in the causal imputation and only slight agreement was found for majority of the tested algorithms. WHO-UMC algorithm showed fair reproducibility and has been suggested as the most consistent tool for causality assessment of ADRs occurring in hospitals in comparison to the Naranjo algorithm which showed slight concordance between the judges.[27]

In this study, WHO-UMC scale was found to be easier to apply and evaluate, and it gave definite results with practical utility when rechallenge was done. On the other hand, Naranjo scale required stringent parameters to be fulfilled, which is difficult to achieve both ethically and economically. It does not consider the role of involvement of other drugs when calculating causality. Though the incidence of CADRs can be estimated from cases identified as definite or probable, establishing causality association with substantial utility in the current scenario of polypharmacy is of utmost importance in advising patient regarding the drugs to avoid. In addition, dechallenge–rechallenge analysis is not possible or permitted for every individual drug that is a part of polypharmacy. Thus, a uniformly acceptable method/scale to ascertain drug causality with practical relevance is desirable.

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Conflicts of interest

There are no conflicts of interest.

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